Removal of thallium by deferasirox in rats as biological model

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ABSTRACT: The present research aimed to characterize the potential efficiency of deferasirox in removing thallium after its administration for 30 days following two dose levels of 20 and 160 µM of thallium (III) chloride to male Wistar rats every day. After thallium administration some abnormal clinical signs such as red staining around the eyes, greenish mottling on the liver, weakness, loss of hair and weight, were observed in animals. Deferasirox was given orally to different groups of rats for a period of one week immediately after thallium administration. After chelation therapy, animals were killed by exsanguination from the abdominal aorta, and then thallium and iron concentrations in various tissues were determined by standard addition method. The chelation therapy results showed that deferasirox was able to remove thallium ions from the body and clinical symptoms were also reduced. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: deferasirox; thallium toxicity; chelation therapy; rats

INTRODUCTION

Thallium, discovered by William Crookes in 1861, is a heavy metal, toxic to humans and animals. The severe toxicity of thallium has been recognized since its discovery in 1861 and, therefore, it has been used as a rodenticide. Despite the World Health Organization's suggestion to ban its use as a pesticide in 1973, which many countries followed, thallium intoxication still occurs worldwide. To mammals, thallium is more toxic than mercury, cadmium, lead, copper or zinc (Lane and Lin, 2005). Ingestion of more than 10–15 mg kg⁻¹ body weight (a dose of about 0.2–1 g) can be lethal (Lech and Sadlik, 2007).

Thallium is expected to exist in its oxidized states, including univalent, Ti(I) and trivalent, Ti(III), species, in the environment. Whereas the elemental form of thallium has essentially no toxicity, its univalent (thallous) and trivalent (thallic) salts are highly toxic (Lane and Lin, 2005). Thallium salts are rapidly and almost completely absorbed by any route, with gastrointestinal exposure being the most common route resulting in toxicity. Unfortunately, awareness of thallium poisoning amongst clinicians is low. Lack of symptoms, or at least non-specific symptoms, at the beginning of intoxication often prevents an early correct diagnosis, and thus the application of appropriate therapeutic measures (Lech and Sadlik, 2007). One of the possible toxic mechanisms of thallium includes ligand formation with blood proteins (Peter and Viraraghavan, 2005; Xiao et al., 2004). Thallium can be released to the environment (Xiao et al., 2004; Heim et al., 2002), exposing humans to its noxious effects. For example, it has been reported that thallium can affect several tissues and systems, including the epidermal, gastrointestinal, cardiovascular, reproductive and renal systems (Heim et al., 2002; Fatemi et al., 2007; Amiri et al., 2007). It can also cross the blood–brain barrier, and deposit in the brain, where it causes neurodegeneration, demyelination and the accumulation of end products of lipid oxidation (Galván-Arzate et al., 2000). One way to remove toxic elements such as thallium from the body is chelation therapy. Chelation therapy involves the use of ligating drugs that bind the metal to treat potentially fatal conditions. These ligands promote the excretion and subsequent depletion of this transition metal in biological systems. Deferasirox (4-(3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl)-benzoic acid, or ICL670, Fig. 1) was first reported in 1999 (Heinz et al., 1999). It is a tridentate chelator with high selectivity for Fe³⁺, and its NO₂⁻ donation arises from one triazole nitrogen and two phenolate oxygen donors (Steinhauser et al., 2004). In vivo, this selectivity is demonstrated by conserved plasma Zn and Cu levels in patients taking deferasirox, and while its efficacy is rather low for inducing negative iron balance, it is effective and well tolerated (Nisbet-Brown et al., 2003). In 2005, deferasirox became the first FDA approved oral alternative for treatment of iron overload and was subsequently approved in the EU in 2006 (Yang et al., 2007). Its relatively long half-life before excretion allows once-daily dosage and good overall patient compliance, as well as cost-effectiveness, and deferasirox is considered to be superior to deferoxamine (DFO). Iron chelation therapy (ICT) with DFO, the current standard for the treatment of iron overload in patients with transfusion-dependent disorders such as β-thalassemia, requires regular subcutaneous or intravenous infusions. This can lead to reduced quality of life and poor adherence, resulting in increased morbidity and mortality in iron overloaded patients with β-thalassemia (Scott and Orvig, 2009).

The aim of this study was to investigate the chelation potency of deferasirox given to animals after thallium loading. Testing was performed using an acute experimental model on rats with the chelator given shortly after thallium administration. This study...